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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/741,534	12/19/2003	Alain Baron	18528.675 / 0218-UTL-9	5134

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Intellectual Property Department
Amylin Pharmaceuticals, Inc.
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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
02/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/741,534	BARON ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11,13-18,28,29,31-38 and 40-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-11, 13-18, 28-29, 31-38, and 40-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/24/2007 has been entered.

Status of the claims

2. According to the amendment to the claims filed 10/24/2007, claims 1-2, 4-11, 13-18, 28-29, 31-38, and 40-56 are pending. Claims 3, 12, 19-27, 30, and 39 are canceled and claims 1, 10, 28, and 37 are amended.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

4. Claims 6 and 7 are objected to as the dependency on claim "1" is actually a capital "I".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-10, 13-18, 28, 31-37, 40-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what the meaning of the recitation "having at least one action of GLP-1" is and thus the meets and bounds of the claims could not be determined. There is no nexus between "at least one function", which could refer to any property of the molecule, such as antibody binding, and a treatment for nephropathy, nor is there any indication of the intended effect. Accordingly, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-11, 13-18, 28-29, 31-38, and 40-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention.

The amended claims are drawn to an analog which include any polypeptide having at least one **action** of GLP-1includes which has at least about 70% sequence homology with an amino acid sequence encoding a base molecule (GLP-1) whether or not including insertions, substitutions, extensions, or deletions. Such analogs may comprise conservative or non-conservative amino acid substitutions (including non-natural amino acids. An "agonist analog," is an analog that exhibits at least one characteristic or action of the base molecule, preferably having potency better than the base molecule, or **within five orders of magnitude (plus or minus) of potency compared to the base molecule**. A "derivative" includes any base molecule or analog having a chemical modification within, attached, linked to, or associated with the molecule. Such chemical modifications can include internal linkers (e.g., spacing or structure-inducing) or appended molecules, such as molecular weight-enhancing molecules (e.g., polyethylene glycol (PEG), polyamino acid moieties, etc.), or tissue targeting molecules. Finally, a "variant" includes any modification to the base molecule not encompassed in the terms "analog" and "derivative" (p. 4-5). However, the specification does not teach any functional variant, fragment, or derivative of the GLP-1 other than the full-length sequence of SEQ ID NO: 1. Some of the Seq. Id. Nos. 2-11, offered by Applicant as examples In the remarks provided in the response to the first non-final rejection and filed on 05/14/2007, Applicant is pointing to the Seq. Id. 2-11 and contends that they constitute adequate written description for a genus of GLP-1 molecules that share a 90% identity with Seq. Id. No.: 1. This argument has been fully

considered but is not deemed persuasive because the claims are not limited to 90% identity, and further, this rejection is based upon lack of enablement commensurate in scope with the claims, and is not on the basis of lack of adequate written description. Even if considering this argument, which is not applicable for all the Seq. Id. Nos. 2-11 since some of the sequences contain more than three possible mutation sites (and the Seq. Id. No.: 1 is 31 amino acids long), the scope of the genus claimed is still considered too broad. At page 14 of the Remarks of 05/14/2007, applicants argue: "...the law provides that experimentation is not necessarily undue simply because it is complex, if the art typically engages in such experimentation." This argument has been fully considered but is not deemed persuasive because the real issue here is that the scope of the claims is too broad, given the definition on analogs and variants and agonists provided in the specification (see supra). Based on that definition one may envision, contrary to the arguments of the applicants, even a new class of compounds since they are defined only by function. There is no working example regarding the method claimed while employing any of the members of the genus for treating nephropathy. There is also a lack of guidance with respect to the conserved structure needed for the activity claimed, the working example being limited to GLP-1. For these reasons it is still maintained that the amount of experimentation needed to establish that the species of the GLP-1 70% identity genus having the activity claimed and which can be used for treatment of nephropathy is undue.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-2, 7, 10, 11, 16, 28, 29, 34, 37, 38, 43, 46-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Momose et al. (U.S. Pat No. 6,251,926).

Momose et al. teach a method of treating diabetic late complications (including nephropathy, hypertension, neuropathy, and retinopathy) using GLP-1 (7-37), in a combination with other drugs, orally or parenterally (injection) (col. 23, lines 6-65; col. 24, lines 54-56; col. 25, lines 1-2; col. 18, lines 26-39).

Since the method of treatment in the claims of the instant application **comprises** administering GLP-1, the claims are anticipated by Momose et al.

8. Claims 1-2, 4-5, 7, 10-11, 13-14, 16, 28-29, 31-32, 34, 37-38, and 40-41, 43, 46-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Knudsen et al.(US 20030144206, 12/23/2002).

Knudsen et al. teach a method for the treatment or prophylaxis of diabetic late complications, such as nephropathy, neuropathy and retinopathy, which method comprises administration of a GLP-1 compound and a modulator of diabetic late

complications to a patient in need thereof ([0015]). The method comprises administration of an effective amount of a GLP-1 compound and administration of an effective amount of a modulator of diabetic late complications. The two compounds may be co-administered or they may be administered separately as two medicaments. Furthermore, the first compound may be administered in a regimen, which additionally comprises treatment with the second compound ([0031]). In a preferred embodiment the GLP-1 compound is a parenteral medicament ([0038]). The dosage of said GLP-1 compound is from 0.1 µg/kg/day to 10 µg/kg/day ([0041-0042]). The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, buccal, pulmonal, transdermal or parenteral [0044].

Since the method of treatment in the claims of the instant application **comprises** administering GLP-1, the claims are anticipated by Knudsen et al.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 4-6, 8-9, 13-15, 17-18, 31-33, 35-36, 40-42, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Momose et al. (U.S. Pat No. 6,251,926).

The teachings of Momose et al. are presented supra. Although Momose et al. teach throughout that therapeutic dosage amounts of the compounds are to be administered, they do not expressly teach the same in terms of µg/kg/day or mg/day of the rejected claims of the instant Application.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use any therapeutic effective amount of the compounds used Momose et al., including dosage and the regimen disclosed by Applicant, because the reference teaches the advantageous use of the same routes of administration (oral or parenterally (injection)) and that it be administered in any therapeutic amount thereof. One of ordinary skill in the art would be motivated to arrive at the present range or specific amounts therein, simply by routine optimization taking into consideration the patient in question and the other factors impacting treatment. Also, given the breadth of the ranges in the claims, there does not appear to be any criticality, and that the claims are inviting the artisan to do the same kind of experimentation that the reference would require. From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference.

12. Claims are 6, 8-9, 15, 17-18, 33, 35-36, 42, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen et al. (US 20030144206, 12/23/2002).

The teachings of Knudsen et al. are presented supra. Knudsen does not explicitly teach the plasma levels and the dosing regimen of the instant rejected claims. Although Knudsen et al. teach therapeutic dosage amounts of the compounds that are to be administered, they do not expressly teach the same in terms of plasma levels and the dosing regimen of the injections of the rejected claims of the instant Application.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use any therapeutic effective amount of the compounds used Knudsen et al., including dosage and the dosing regimen disclosed by Applicant, because the reference teaches the advantageous use of the same routes of administration (oral or parenterally (injection)) and that it be administered in any therapeutic amount thereof. One of ordinary skill in the art would be motivated to arrive at the present range or specific amounts therein, simply by routine optimization taking into consideration the patient in question and the other factors impacting treatment. From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the reference.

13. Claims 1-2, 4-11, 13-18, 28-29, 31-38, and 40-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coolidge et al. (WO 01/89554, 11/29/2001), in view of Holst et al. (WO 02/085406, 04/24/2002) and in further view of Guitard et al. (US 2001/0016586, 08/23/2001).

The claims are drawn to a method for preventing or treating a subject having nephropathy or for preventing progression to ESRD or of reducing proteinuria in a patient (claims 28 and 29), or for preventing or slowing progression of glomerulosclerosis (claims 37 and 38), comprising: administering to an individual in need of such treatment an effective amount of a compound which is a GLP-1 or a biologically active agonist, analog, derivative, variant, or fragment of it. Each of the main claims is further limited by dosage, rate of administration and mode of administration.

Coolidge et al. teach a method of treatment, using GLP-1, of an individual with cardiac abnormalities consistent with ischemic heart disease (p. 28, lines 5-18). The continuous administration doses taught are 0.1-10 pmol/kg/min, or from 0.5-50 pmol/kg/min, for subcutaneous administration (p 19, lines 22-26), which are well within the limits of the claims of the instant application. The parenteral administration route of the instant claims could be any of the intravenous or subcutaneous routes of Coolidge at al. The biological properties of the GLP-1 are intrinsically related to its structure and its function is inherent. As correctly pointed out by the Applicant, Coolidge did not

specifically teach treating nephropathy, treating End Stage Renal Disease (ESRD), improving endothelial function, reducing proteinuria, or slowing progression of glomerulosclerosis with GLP- 1. Given the breadth of the ranges in the claims, there does not appear to be any criticality, and that the claims are inviting the artisan to do the same kind of experimentation that the reference would require. Contrary to the assertion of the applicant, in the Remarks filed on 10/24/2007, that Coolidge et al does not disclose how or why GLP-1 treats ischemic heart disease (IHD), Coolidge et al. offers such explanations on page 2, lines7-22, which clearly show that excess glucagon may lead to myocardial tissue damage and GLP-1, which is an antagonist, was used to treat an ischemic patient which was incapable of auto-regulation of blood glucose. The same mechanism of action is present in the renal tissue, where excess glucose due to the diabetes will damage the renal cells and lead to nephropathies and may lead to ESRD.

. However, the GLP-1 molecule of the invention of Coolidge et al. would bind and exert its action irrespective of the condition sought to be treated.

GLP-1 and analogs were previously known in the art for their use to treat diabetes, as acknowledged by the Applicant in the specification and in the Remarks (e.g. U.S. Pat. 5,574,008-which teaches a method of treating diabetes with GLP-1 analogs). The definition of the ESRD, end-stage renal disease (provided in the Final Office action of 07/25/2007) clearly present as an etiological cause diabetes, and hypertension which both can be treated by GLP-1as proved by Holst et al.

Holst et al. teach treating insulin resistance-associated conditions with GLP-1 (p. 4, lines 6-10). Manifestations of the insulin resistance syndrome include hypertension albuminuria both related to renal function.

Guitard et al. teach the use of GLP-1, as a hypoglycemic agent, in nephropathies, peripheral angiopathies, hypertension, microangiopathic changes, diabetes and insulin resistance.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of Coolidge et al. with the teachings of Holst et al and Holst et al. to treat nephropathy patients with a reasonable expectation of success because Coolidge et al. treats ischemic heart disease with GLP-1 and thus inherently blocks the action of glucagon and treats insulin resistance as, taught by Holst et al. The expectation of success is reasonable when combined Guitard's et al. teachings of using GLP-1 in nephropathies. Therefore, when considering the subject matter as a whole, it would have been *prima facie* obvious to one of skill in the art to modify the methods taught by Coolidge et al. to be used in the diseases taught by Guitard et al. and Holst et al. with a reasonable expectation of success.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As presented supra, the motivation is always present to a skilled artisan that uses known options available to him to optimize a process or a formulation, as eloquently expressed

in the Supreme Court decision in KSR International Co. v. Teleflex Inc., 550 US, 82 USPQ2d 1385 (2007).

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Yu et al., J Hypertension 21, 1125-1135, 2003., Parkes et al. Metabolism, 50, 583-589, 2001.

Yu et al. discuss the antihypertensive effects of GLP-1 while Parkes et al. disclose the insulinotropic effects of GLP-1.

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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/Lorraine Spector/

Primary Examiner, Art Unit 1647